

# Asymptotic Behaviour of the Rate of Adaptation

Feng Yu, Alison Etheridge and Charles Cuthbertson

**Abstract:** We consider the accumulation of beneficial and deleterious mutations in large asexual populations. The rate of adaptation is affected by the total mutation rate, proportion of beneficial mutations, and population size  $N$ . We show that regardless of mutation rates, as long as the proportion of beneficial mutations is strictly positive, the adaptation rate is at least  $\mathcal{O}(\log^{1-\delta} N)$  where  $\delta$  can be any small positive number, if the population size is sufficiently large. This shows that if the genome is modeled as continuous, there is no limit to natural selection, i.e. the rate of adaptation grows in  $N$  without bound.

**AMS 2000 subject classifications:** Primary: 92D15; Secondary: 82C22, 60J05, 92D10; Key words: adaptation rate, natural selection, evolutionary biology, Moran particle systems.

## 1. Background and Introduction

We consider the accumulation of mutations in large asexual populations. The mutations that biological organisms accumulate over time can be classified into three categories: beneficial, neutral, and deleterious. Beneficial mutations increase the fitness of the individual carrying the mutation, while deleterious mutations decrease fitness; neutral mutations have no effect on fitness. Adaptation is driven by accumulation of beneficial mutations, but it is limited by *clonal interference* (clones that carry different beneficial mutations compete with each other and interfere with the other's growth in the population). Fisher and Muller argued for the importance of this effect as early as the 1930s (Fisher 1930, Muller 1964). Here we are concerned with the rate of adaptation, that is the rate of increase of mean fitness in the population.

The simplest scenario one can consider is one in which a single beneficial mutation arises in an otherwise neutral population and no further mutations occur until the fate of that mutant is known. This situation is well understood. The most basic question one can ask is what is  $p_{fix}$ , the fixation probability of the mutation. This was settled by Haldane (1927), who showed that under a discrete generation haploid model, if the selection coefficient associated with the mutation is  $s$ , then under these circumstances  $p_{fix} \approx 2s$ . In this case  $p_{fix}$  is almost independent of the population size,  $N$ .

---

\*CC supported by EPSRC DTA, FY supported by EPSRC/GR/T19537 while at the University of Oxford. Affiliated Institutions: Charles Cuthbertson, Morgan Stanley, 20 Bank Street, London, E14 4AD, UK; Alison Etheridge, Department of Statistics, University of Oxford, 1 South Parks Road, Oxford, OX1 3TG, UK; Feng Yu, School of Mathematics, University of Bristol, University Walk, Bristol, BS8 1TW, UK.



When the mutation does fix, the process whereby it increases in frequency from  $1/N$  to 1 is known as a *selective sweep*. The duration of a selective sweep is  $\mathcal{O}(\log(sN)/s)$  generations. If one assumes that the mutation rate per individual per generation is  $\mu$ , then the overall mutation rate will be proportional to population size and we see that for large populations the assumption that no new mutation will arise during the timecourse of the sweep breaks down. Instead one expects multiple overlapping sweeps. In an asexual population mutations can only be combined if they occur sequentially within the same lineage. This means that, on the one hand, alleles occurring on the same lineage can boost one another's chance of fixation, but on the other hand alleles occurring on distinct lineages competitively exclude one another. The net effect is to slow down the progress of natural selection. This is an extreme form of the Hill-Robertson effect. Hill and Robertson (1966) were the first to quantify the way in which linkage between two sites under selection in a finite population (whether sexually or asexually reproducing) limits the efficacy of natural selection. In a sexually reproducing population, recombination breaks down associations between loci and so ameliorates the Hill-Robertson effect, suggesting an indirect selective force in favour of recombination. Further quantitative analysis of the interference between selected loci is provided by Barton (1995) who considers the probability of fixation of two favourable alleles in a sexually reproducing population. His method is only valid if the selection coefficient of the first beneficial mutation to arise is larger than that of the second. Yu *et al.* (2008) consider the same question in the general setting. The conclusion from both works is that fixation probabilities are reduced, sometimes drastically, because of interference between the two mutations. Furthermore, if the second mutation is stronger than the first, then Yu *et al.* (2008) show that the strength of interference can be strongly dependent on population size. In this work we do not consider the effects of recombination, since we only work with asexual populations.

Since all beneficial mutations eventually become either extinct or ubiquitous in the population, the rate of adaptation, defined to be the rate of increase of the mean fitness of the population, is proportional to  $\mu s p_{fix} N$ , where  $\mu N$  is the total number of beneficial mutations that occur to all individuals in the population in a single generation and we assume  $p_{fix}$  to be the same for all beneficial mutations, which is the case for the system in stationarity. If  $p_{fix}$  is independent of population size, then we expect an adaptation rate of  $\mathcal{O}(N)$ . However, as explained above, the occurrence of simultaneous selective sweeps reduces  $p_{fix}$  and so  $p_{fix}$  may not be  $\mathcal{O}(1)$ . This leads to the following question: if one does not limit the number of simultaneous selective sweeps, what is  $p_{fix}$ , or equivalently, what is the rate of adaptation? As  $N \rightarrow \infty$ , is the rate of adaptation finite or does it increase without bound? There has been some controversy surrounding this question. Some work (e.g. Barton & Coe 2007) suggests that there is an asymptotic limit to the rate of adaptation. Other authors (e.g. Rouzine *et al.* 2003, Wilke 2004, and Desai & Fisher 2007) argue that no such limit exists. Here we study this problem in a mathematically rigorous framework.

Previous work on this question has adopted two general approaches: (i) calculate the fixation probability  $p_{fix}$  directly, and (ii) study the distribution of fitness



of all individuals in the population and asks how this distribution evolves with time. The first approach was used in Gerrish & Lenski (1998), Wilke (2004) and Barton & Coe (2007). Gerrish & Lenski (1998) were the first to present a quantitative analysis of the rate of adaptation in the presence of clonal interference. They obtained approximate integral expressions for the fixation probability of a beneficial mutation and thus the expected rate of adaptation. Orr (2000) generalised the results of Gerrish & Lenski (1998) to include the effects of deleterious mutations. Wilke (2004) combined the works of Gerrish & Lenski (1998) and Orr (2000) to obtain approximate expressions for the adaptation rate that grow logarithmically or doubly logarithmically for large  $N$ . In all three works, the authors used a sequence of approximations before arriving at an expression for the fixation probability or the adaptation rate. It seems to be highly non-trivial to turn any of these approximation steps into a rigorous mathematical argument and so we do not follow their approaches here.

The second approach, to consider the distribution of fitness in the population, was used in Rouzine *et al.* (2003), Brunet *et al.* (2006), and Rouzine *et al.* (2007). As in the work described in the last paragraph, Rouzine *et al.* (2003) take fitness effects to be additive, but whereas before the selection coefficient of each new mutation was chosen from a probability distribution, now all selection coefficients are taken to be equal. In this setting a beneficial and a deleterious mutation carried by the same individual cancel one another out and an individual's fitness can be characterised by the *net* number of beneficial mutations which it carries (which may be negative). Writing  $P_k$  for the proportion of individuals with fitness equivalent to  $k$  beneficial mutations,  $\{P_k\}_{k \in \mathbb{Z}}$  forms a type of *traveling wave* whose shape remains basically unchanged over time. The position of the wave moves to the left or the right on the fitness axis, depending on whether the adaptation rate is positive or negative. This is similar to traveling waves arising from reaction-diffusion equations in the PDE literature (see e.g. Chapter 15 of Taylor (1996)). In the current setting, however, the shape of the wave actually fluctuates stochastically even after a long time. So the wave can be regarded as a stochastic traveling wave, and its *speed* is proportional to the rate of adaptation. Rouzine *et al.* (2003) studied a multilocus model that does not include recombination but does include beneficial, deleterious, and compensating mutations. They found that the rate of adaptation (i.e. the speed of the traveling wave) asymptotically depends logarithmically on population size  $N$ , which is consistent with results of *in vitro* studies of a type of RNA virus in Novella *et al.* (1995) and Novella *et al.* (1999). Rouzine *et al.* (2007) presents the same approach but with more detailed derivations and improved treatments of the stochastic edge.

Desai and Fisher (2007) also adopts the traveling wave approach. Their method of studying the adaptation rate, however, differs from that of Rouzine *et al.* (2003) and Rouzine *et al.* (2007) in that they consider the fitness variation of the population to be in mutation-selection balance, and ask how much variance in fitness can the population maintain while this variation is being selected on. The conclusion they reach is that this variation (hence the adaptation rate) increases logarithmically with both population size and mutation rate.



Brunet *et al.* (2006) study a model in which each of the  $N$  individuals in the population gives birth to  $k$  offspring, each of which has a fitness that differs from the fitness of its parent by a random amount and finally the  $N$  fittest individuals are used to form the next generation. This model resembles artificial selection, rather than natural selection, but it may be easier to study because the density of individuals of a certain fitness in the next generation has a kind of *local dependence* on that density in the current generation. This is quite different from the behaviour considered in Rouzine *et al.* (2003) and our work in this article, where the density of individuals of a given fitness depends on the whole fitness distribution of the parental population.

This work originally arose from discussions with Nick Barton and Jonathan Coe which focused on limits to the rate of adaptation when all mutations are beneficial. In reality, most mutations are either neutral or deleterious. In particular, if all mutations in an asexual population were deleterious, then the population would irreversibly accumulate deleterious mutations, a process known as Muller's ratchet. The first mathematically rigorous analysis of Muller's ratchet is due to Haigh (1978). There a Wright-Fisher model is formulated that incorporates the effects of selection and mutation. Again all mutations carry equal weight so that individuals can be classified according to how many mutations they carry. Haigh (1978) showed that if the population size is infinite (so that the dynamics of the model become deterministic) then there is a stationary distribution. In the finite population case, however, this is not the case. At any given time there is a *fittest class*, corresponding to those individuals carrying the smallest number of mutations, but this class will eventually be lost due to genetic drift (the randomness in the reproduction mechanism). This loss is permanent since there is no beneficial or back mutation to create a class fitter than the current fittest class. The next fittest class then becomes the fittest class, but that will be lost eventually as well and the entire population grows inexorably less fit. Higgs & Woodcock (1995) derived a set of moment equations for Haigh's model but these are not closed and so are hard to analyse. Instead, their results rely mainly on simulations. Stephan *et al.* (1993) and Gordo & Charlesworth (2000) use (slightly different) one-dimensional diffusions to approximate the size of the fittest class. Etheridge *et al.* (2007) go much further along this line (and provide a more thorough review of the literature than that included here). They conjecture and provide justification for a phase transition and power law behaviour in the rate of the ratchet. But in spite of the very considerable body of work on Muller's ratchet, even a rigorous expression for the rate of decline in mean fitness of the population remains elusive.

Muller's ratchet caricatures the evolution of a population in which there is no recombination and no beneficial mutation. Such a population is doomed to become progressively less and less fit. So how can a species overcome the ratchet? If it reproduces sexually, then recombination of parental chromosomes can create offspring that are fitter than either parent and so Muller's ratchet has been proposed as an explanation for the evolution of sexual reproduction (e.g. Muller 1964, Felsenstein 1974). But not all populations reproduce sexually. Another mechanism which has the potential to overcome Muller's ratchet is the



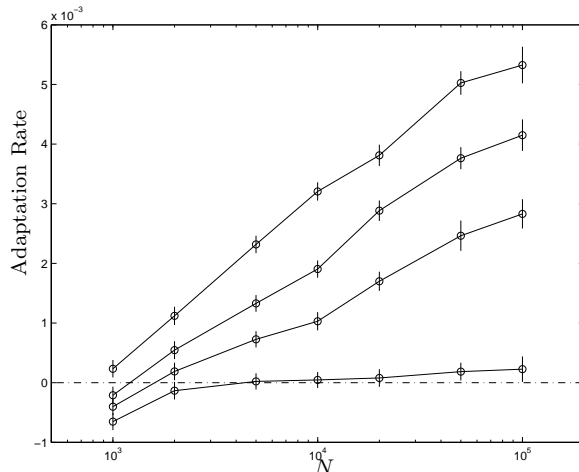


FIG 1. Adaptation rate against population size, from top to bottom, for  $q = 4\%$ ,  $2\%$ ,  $1\%$  and  $0.2\%$ ,  $\mu = 0.01$ , and  $s = 0.01$ . Circles represent data points obtained from simulation,  $q$  is the probability that a mutation is advantageous, and vertical bars represent one standard deviation.

presence of beneficial mutations, and it is this mechanism that we shall consider here. More specifically, we pose the following question: with both beneficial and deleterious mutations, does a sufficiently large population overcome Muller’s ratchet?

The conclusion we reach, through both non-rigorous (§3) and rigorous (Theorem 4.6) approaches, is the following: as long as the proportion of beneficial mutations is strictly positive, the rate of adaptation is roughly  $\mathcal{O}(\log N)$  for large  $N$ , where  $N$  is the population size and time is measured in generations. This shows that even with a tiny proportion of beneficial mutations, a large enough population size will yield a positive adaptation rate, in which case the entire population grows fitter at a high rate and Muller’s ratchet is overcome. It also shows, in particular, that the rate of adaptation grows without bound as  $N \rightarrow \infty$  in the all-mutations-beneficial case. This is consistent with the findings of Rouzine *et al.* (2003) and Wilke (2004).

Figure 1 plots the adaptation rate against log population size from simulation results of the model we consider in this article. We observe that for each set of parameters  $q$ ,  $\mu$  and  $s$ , the rate of adaptation is roughly proportional to  $\log N$  and small population sizes may result in negative adaptation rates. Furthermore, larger  $q$  results in a higher adaptation rate for fixed  $\mu$  and  $s$ . The upshot is that with  $\mu$  and  $s$  held constant, a smaller proportion of beneficial mutations needs a larger population size for Muller’s ratchet to be overcome.

In the model we study here the selection coefficient  $s$  is held fixed as  $N \rightarrow \infty$ . This is known as a ‘strong selection’ model. Our interest is in the behaviour of the model for very large  $N$ . It is not clear in this setting how to pass to an



infinite population limit and so we must work with a model based on discrete individuals. An alternative model, the so-called weak selection model, is used to address behaviour of very large populations when  $Ns$  is not too large. By fixing  $Ns$  (as opposed to  $s$ ) one can pass to an infinite population limit. The limiting model comprises a countably infinite system of coupled stochastic differential equations for the frequencies of individuals of different fitnesses within the population. Preliminary calculations for this model are presented in Yu and Etheridge (2008).

This work is organised as follows. In §2, we formulate our model. In the biological literature one would expect to see a Wright-Fisher model, but since we are interested in large populations, we expect the same results for the much more mathematically tractable Moran particle model which we describe. We also perform some preliminary calculations. In §3, we present a non-rigorous argument that leads to an asymptotic adaptation rate of roughly  $\mathcal{O}(\log N)$ . In §4, we present and prove our main rigorous result that establishes a lower bound of  $\log^{1-\delta} N$  for any  $\delta > 0$  on the adaptation rate. And finally in §5, we prove the supporting lemmas required for the proof of our main theorem.

## 2. The Finite Population Moran Model

We assume constant population size  $N$ . For each  $N \in \mathbb{N}$ , let  $X_i(t) \in \mathbb{Z}$ ,  $i = 1, \dots, N$ , denote the *fitness type* of the  $i^{\text{th}}$  individual, defined to be the number of beneficial mutations minus the number of deleterious mutations carried by the individual. For  $k \in \mathbb{Z}$ , let  $P_k(t)$  denote the proportion of individuals that have fitness type  $k$  at time  $t$ , i.e.

$$P_k = \frac{1}{N} \sum_{i=1}^N \mathbf{1}_{\{X_i=k\}}.$$

We use  $\mathcal{P}^{(N)}(\mathbb{Z})$  to denote the space of probability measures  $p$  on  $\mathbb{Z}$  formed by  $N$  point masses each with weight  $1/N$ , and define

$$S^{(N)} = \mathcal{P}^{(N)}(\mathbb{Z})$$

to be the state space for  $P_k(t)$ . For  $p \in S^{(N)}$ , we define  $p_k = p(\{k\})$  and

$$\begin{aligned} p_{[k,l]} &= \sum_{i=k}^l p_i \\ m(p) &= \langle k, p \rangle = \sum_{k \in \mathbb{Z}} k p_k \\ c_n(p) &= \sum_{k \in \mathbb{Z}} (k - m(p))^n p_k. \end{aligned} \tag{1}$$

In particular,  $m(p)$  is the mean fitness of the population, and  $c_2(p) = \langle k^2, p \rangle - \langle k, p \rangle^2$  is the 2<sup>nd</sup> central moment of the population fitness, i.e. its variance. We



sometimes abuse notation and use  $P$  to denote the probability mass function of different fitness types associated with the probability measure  $P$ .

The model of interest is one where each individual accumulates beneficial mutations at a Poisson rate  $q\mu$  and deleterious mutations at rate  $(1 - q)\mu$ . We assume a so-called infinitely-many-loci model where each mutation is assumed to be new and occur at a different locus on the genome. All individuals experience selection effects via a selection mechanism (which introduces a drift reflecting the differential reproductive success based on fitness) and the effect of genetic drift via a resampling mechanism. The mechanisms of this model are described below:

1. *Mutation*: For each individual  $i$  a mutation event occurs at rate  $\mu$ . With probability  $1 - q$ ,  $X_i$  changes to  $X_i - 1$  and with probability  $q$ ,  $X_i$  changes to  $X_i + 1$ .
2. *Selection*: For each pair of individuals  $(i, j)$ , at rate  $\frac{s}{N}(X_i - X_j)^+$ , individual  $i$  replaces individual  $j$ .
3. *Resampling*: For each pair of individuals  $(i, j)$ , at rate  $\frac{1}{N}$ , individual  $i$  replaces individual  $j$ .

This model has a time scale such that one unit of time corresponds roughly to one generation. A more sophisticated model should consider mutations that have a distribution of fitness effects, e.g. an independent exponentially distributed selective advantage associated with each new beneficial mutation as proposed by Gillespie (1991). Recent work by Hegreness *et al.* (2006), however, suggests that in models where beneficial mutations have a distribution of fitness advantages, evolutionary dynamics, e.g. the distribution of successful mutations which ultimately determines the rate of adaptation, can be reasonably described by an equivalent model where all beneficial mutations confer the same fitness advantage. One can also describe the mechanisms in the above model in terms of the  $P_k$ 's,

1. *Mutation*: for any  $k \in \mathbb{Z}$ , at rate  $(1 - q)\mu N P_k$ ,  $P_k$  decreases by  $\frac{1}{N}$  and  $P_{k-1}$  increases by  $\frac{1}{N}$ ; at rate  $q\mu N P_k$ ,  $P_k$  decreases by  $\frac{1}{N}$  and  $P_{k+1}$  increases by  $\frac{1}{N}$ .
2. *Selection*: for any pair of  $k, l \in \mathbb{Z}$  such that  $k > l$ , at rate  $s(k - l)N P_k P_l$ ,  $P_k$  increases by  $\frac{1}{N}$  and  $P_l$  decreases by  $\frac{1}{N}$ .
3. *Resampling*: for any pair of  $k, l \in \mathbb{Z}$ , at rate  $N P_k P_l$ ,  $P_k$  increases by  $\frac{1}{N}$  and  $P_l$  decreases by  $\frac{1}{N}$ .

We use  $(P, X)$  to denote the process evolving under the above mechanism, where  $X$  describes the fitness types of the  $N$  exchangeable individuals and  $P$  describes the empirical measure formed by the fitness types of these individuals. If there is no confusion, we drop  $X$  and denote the process simply by  $P$ . The main result of this work, Theorem 4.6, states that under the above model, the mean fitness increases at a rate of at least  $\mathcal{O}(\log^{1-\delta} N)$  for any  $\delta > 0$  after a sufficiently long time.

**Remark 2.1.** Notice that the resampling acts on ordered pairs, so that the



overall rate at which an individual is affected by a resampling event is  $2N$  and at such an event it has equal chance of reproducing or dying. It would be more usual to have resampling at half this rate, but this choice of timescale does not change the results and will save us many factors of two later.

Often one combines the resampling and selection into a single term. Each pair of individuals is involved in a reproduction event at some constant rate and the effect of selection is then that it is more likely to be the fitter individual that reproduces. Since  $s$  is typically rather small, our simpler formulation is a very small perturbation of this model and again the statement of our results would not be changed in that framework.

**Remark 2.2.** We take the selection mechanism to be additive instead of multiplicative, i.e. the fitness type of an individual with  $k$  beneficial mutations is  $1 + sk$  instead of  $(1 + s)^k$ . Even though  $(1 + s)^k \approx 1 + sk$  is only valid for small  $s$  and  $k$ ,  $(1 + s)^k \geq 1 + sk$  holds for all  $s \in [-1, \infty)$ , thus our main result of a lower bound on the rate of adaptation also holds for multiplicative selection effects.

One can construct the process  $X(t)$  using Poisson random measures and Poisson processes. More specifically, let  $l$  denote the Lebesgue measure on  $\mathbb{R}$ . For each  $i \in \mathbb{Z}$ , let  $\Lambda_{1i,b}^{(N)}$  and  $\Lambda_{1i,d}^{(N)}$  be independent Poisson processes with intensities  $q\mu$  and  $(1 - q)\mu$ , respectively. For each  $i, j \in \mathbb{Z}$ , let  $\Lambda_{2ij}^{(N)}$  be a Poisson random measure on  $\mathbb{R}^+ \times \mathbb{R}^+$  with intensity measure  $\frac{1}{N}l \times l$ . And, for each  $i, j \in \mathbb{Z}$ , let  $\Lambda_{3ij}^{(N)}$  be a Poisson process with intensity  $\frac{1}{N}$ . Then  $X_i$  satisfies the following jump equation:

$$\begin{aligned} X_i(t) = & X_i(0) + \int_0^t \Lambda_{1i,b}^{(N)}(du) - \int_0^t \Lambda_{1i,d}^{(N)}(du) \\ & + \sum_j \int_{[0,t] \times [0,\infty)} (X_j(u-) - X_i(u-)) \mathbf{1}_{\{\xi \leq s(X_j(u-) - X_i(u-))\}} \Lambda_{2ij}^{(N)}(du, d\xi) \\ & + \sum_j \int_0^t (X_j(u-) - X_i(u-)) \Lambda_{3ij}^{(N)}(du). \end{aligned} \quad (2)$$

In the above, jumps of  $\Lambda_{3ij}^{(N)}$  give possible times when the type of individual  $i$  is replaced by that of individual  $j$  due to the resampling mechanism; jumps of  $\Lambda_{2ij}^{(N)}$  give possible times when the type of individual  $i$  is replaced that of individual  $j$  due to the selection mechanism; and jumps of  $\Lambda_{1i,b}^{(N)}$  and  $\Lambda_{1i,d}^{(N)}$  give possible times when the type of individual  $i$  increases and decreases by 1 due to the beneficial and deleterious mutation mechanisms, respectively.

In terms of  $P_k$ , we have

$$\begin{aligned} P_k(t) = & P_k(0) + \mu \int_0^t qP_{k-1}(u) - P_k(u) + (1 - q)P_{k+1}(u) du \\ & + s \int_0^t \sum_{l \in \mathbb{Z}} (k - l)P_k(u)P_l(u) du + M_k^{P,1}(t) + M_k^{P,2}(t) \end{aligned} \quad (3)$$



where  $M_k^{P,1}$  and  $M_k^{P,2}$  are orthogonal martingales, the first arising from the (compensated) mutation mechanism and the second from the resampling and selection mechanisms.

We define the conditional quadratic variation of an  $L^2$ -martingale  $(M_t)_{t \geq 0}$  to be the unique previsible process  $\langle M \rangle(t)$  that makes  $M(t)^2 - M(0)^2 - \langle M \rangle(t)$  a martingale. See e.g. Chapters II.6 and III.5 of Protter (2003). With this notation, following the method of, for example, Ikeda & Watanabe (1981), §II.3.9 we obtain

$$\begin{aligned}
\langle M_k^{P,1} \rangle(t) &= \frac{\mu}{N} \int_0^t q P_{k-1}(u) + P_k(u) + (1-q) P_{k+1}(u) du \\
\langle M_k^{P,1}, M_{k-1}^{P,1} \rangle(t) &= -\frac{\mu}{N} \int_0^t q P_{k-1}(u) + (1-q) P_k(u) du \\
\langle M_k^{P,1}, M_l^{P,1} \rangle(t) &= 0 \text{ if } |k-l| \geq 2 \\
\langle M_k^{P,2} \rangle(t) &= \frac{1}{N} \int_0^t \sum_{l \in \mathbb{Z}} (2 + s|k-l|) P_k(u) P_l(u) du \\
\langle M_k^{P,2}, M_l^{P,2} \rangle(t) &= -\frac{1}{N} \int_0^t (2 + s|k-l|) P_k(u) P_l(u) du \\
&\quad \text{if } k \neq l.
\end{aligned} \tag{4}$$

With the expressions in (3) and (4), we can write the martingale decomposition of the mean  $m(P(t)) = \sum_k k P_k(t)$  in the notation of (1) as follows

$$\begin{aligned}
m(P(t)) &= m(P(0)) + \mu \int_0^t \sum_k k [q P_{k-1}(u) - P_k(u) + (1-q) P_{k+1}(u)] du \\
&\quad + s \int_0^t \sum_{k,l \in \mathbb{Z}} k(k-l) P_k(u) P_l(u) du + M^{P,m}(t) \\
&= m(P(0)) + \mu(2q-1)t + s \int_0^t c_2(P(u)) du + M^{P,m}(t)
\end{aligned}$$

where  $M^{P,m}$  is a martingale, or in differential notation,

$$dm(P) = (\mu(2q-1) + s c_2(P)) dt + dM^{P,m}. \tag{5}$$

### 3. A Non-rigorous Argument

In this section, we give a non-rigorous argument that leads to an asymptotic adaptation rate of roughly  $\mathcal{O}(\log N)$ , as long as  $q$  is strictly positive and regardless of the selection and mutation parameters. A rigorous argument in §4 will establish a lower bound of  $\mathcal{O}(\log^{1-\delta} N)$  on the adaptation rate.

Our non-rigorous approach is similar to that of Rouzine *et al.* (2003). We assume the ‘bulk’ of the wave, i.e. at  $k$ ’s not too far away from the mean fitness,



behaves like a deterministic traveling wave and obtain an approximate expression for the shape of this wave. More specifically, we obtain a set of equations satisfied by all central moments of the distribution  $P$ , which will dictate that the wave is approximately Gaussian. There is, however, an infinite family of solutions to these equations, parameterised by the variance of  $P$ , which ultimately determines the wave speed. To determine the correct wave speed for a given parameter set (i.e. population size, mutation and selection coefficients, and the proportion of beneficial mutations), we use the essentially stochastic behaviour at the front of the wave to calculate the wave speed. The answer we obtain from both calculations, i.e. using the ‘bulk’ and the front of the wave, must be the same. This constraint will yield an approximate expression for the adaptation rate.

With all martingale terms in (3) of order  $P/N$ , the effect of noise on  $P_k$  can be considered to be quite small if  $P_k$  is much larger than  $1/N$ . For  $k$ ’s where  $P_k$  is in this range, we have from (3),

$$\begin{aligned} dP_k &\approx \left[ \mu(qP_{k-1} - P_k + (1-q)P_{k+1}) + s \sum_{l \in \mathbb{Z}} (k-l)P_k P_l \right] dt \\ &= [\mu(qP_{k-1} - P_k + (1-q)P_{k+1}) + s(k - m(P))P_k] dt. \end{aligned} \quad (6)$$

This is similar to Equation (2) in Rouzine *et al.* (2003).

If we assume that  $\{P_k\}_{k \in \mathbb{Z}}$  evolves according to this deterministic system, then we can calculate the central moments via the Laplace transform  $\psi(\theta; p) = \sum_k e^{\theta(k-m(p))} p_k$ :

$$d\psi(\theta) = \sum_k e^{\theta(k-m(P))} dP_k - \sum_k \theta e^{\theta(k-m(P))} P_k dm(P).$$

Furthermore, we can obtain from (5)

$$dm(P) \approx (\mu(2q-1) + sc_2(P)) dt. \quad (7)$$

Therefore

$$\begin{aligned} d\psi(\theta) &\approx \left[ \mu \sum_k e^{\theta(k-m(P))} (qP_{k-1} - P_k + (1-q)P_{k+1}) \right. \\ &\quad \left. + s \sum_k e^{\theta(k-m(P))} (k - m(P))P_k \right. \\ &\quad \left. - \sum_k \theta e^{\theta(k-m(P))} P_k (\mu(2q-1) + sc_2(P)) \right] dt \\ &= [\psi(\theta)(\mu(qe^\theta - 1 + (1-q)e^{-\theta}) - \theta(\mu(2q-1) + sc_2(P))) + s\psi'(\theta)] dt \\ &= [\psi(\theta)(\mu(qe^\theta - 1 + (1-q)e^{-\theta}) - \theta(2q-1)) - \theta sc_2(P) + s\psi'(\theta)] dt. \end{aligned}$$

We observe that the term with coefficient  $\mu$  is  $\mathcal{O}(\theta^2)$ , thus for small  $\theta$ , the effect of the mutation mechanism on the centred wave is relatively small compared to the



selection mechanism. We drop the terms arising from the mutation mechanism to obtain

$$d\psi(\theta) \approx s [-\psi(\theta)\theta c_2(P) + \psi'(\theta)] dt.$$

Differentiating this repeatedly and using the fact that  $c_n(P) = \psi^{(n)}(0; P)$  for  $n \geq 2$  we obtain the following approximate system for the central moments  $c_n$ :

$$dc_n(P) \approx s(c_{n+1}(P) - nc_{n-1}(P)c_2(P)) dt.$$

If we assume the shape of the wave to be roughly deterministic and stationary, then setting the expressions on the right hand side to zero we see that the central moments of  $P$  satisfies

$$c_n(P) = \begin{cases} 0, & \text{if } n \geq 3 \text{ is odd} \\ \frac{(2n)!}{2^n n!} c_2(P)^{n/2}, & \text{if } n \geq 2 \text{ is even} \end{cases},$$

which are the central moments of normal distribution with variance  $c_2(P)$ . Hence  $P$  is approximately Gaussian, but the variance is not determined.

We can use this information to guess at the asymptotic variance of the wave, which will also, through Equation (7) yield an expression for the asymptotic rate of adaptation. We follow §3 of Yu & Etheridge (2008) and assume that  $P$  is approximately Gaussian with mean  $m(P)$  and variance  $b^2$ , and the ‘front’ of the wave is approximately where the level of  $P$  falls to  $1/N$ . If the front of the wave is at  $K + m(P)$ , then

$$\frac{1}{2\pi b^2} e^{-K^2/2b^2} = \frac{1}{N},$$

hence

$$K \approx b\sqrt{2\log N}. \quad (8)$$

To estimate how long it takes the wave to advance by one, we suppose that a single individual is born at  $K + m(P)$  at time zero and estimate the time it takes for an individual to be born at  $K + m(P) + 1$ . Let  $Z(t)$  be the number of individuals at site  $K + m(P)$  at time  $t$ . Note that these are the fittest individuals in the population. According to (6), until a beneficial mutation falls on site  $K + m(P)$ ,  $Z(t)$  increases exponentially at rate  $sK - \mu$ . Ignoring beneficial mutations occurring to type  $K - 1 + m(P)$ , i.e.

$$Z(t) \approx e^{(sK - \mu)t}. \quad (9)$$

As the population at site  $K + m(P)$  grows, each individual accumulates beneficial and deleterious mutations at rates  $q\mu$  and  $(1 - q)\mu$  respectively. The occurrence of the first beneficial mutation will result in the advance of the wavefront. Using (9), we deduce that the probability that no beneficial mutation occurs to any individuals with fitness type  $K + m(P)$  by time  $t$  is

$$\exp \left\{ -q\mu \int_0^t Z(u) du \right\} = \exp \left\{ -\frac{q\mu}{sK - \mu} (e^{(sK - \mu)t} - 1) \right\},$$



which gives a wave speed of  $(sK - \mu)/\log(sK - \mu)$ .

Now we equate the results of our two calculations for the wave speed. By (7), the wave speed is  $\mu(2q-1) + sc_2(P) = \mu(2q-1) + sb^2 \approx \mu(2q-1) + sK^2/(2\log N)$ , using the equality involving  $K$  and  $b$  in (8). This leads to the following consistency condition:

$$\frac{sK - \mu}{\log(sK - \mu)} = \mu(2q - 1) + \frac{sK^2}{2\log N}.$$

For large  $K$ , this approximately reduces to

$$K \log(sK) = 2\log N. \quad (10)$$

It is easy to see that  $K$  must be smaller than  $\log N$  but larger than any fractional power of  $\log N$ . In fact, (10) is a transcendental equation whose solution can be written as  $K = \frac{1}{\sigma} W(N^{2\sigma})$ , where  $W(z) : [0, \infty) \rightarrow [0, \infty)$  is the inverse function of  $z \mapsto ze^z$ . Corless *et al.* (1996) calls the function  $W$  the Lambert  $W$  function, and gives useful asymptotic expansion results of this function near 0 and  $\infty$ , e.g. Equation (4.20) of Corless *et al.* (1996). In particular, the two leading terms of this expansion are

$$W(z) = \log z - \log \log z + \dots,$$

which shows that  $K = 2\log N - \log(2\log N) + \dots$  and the leading term of the wave speed is  $2\sigma \log N / (\log \log N)$ . Our rigorous results in §4 will show that the rate of adaptation is asymptotically greater than any fractional power of  $\log N$  as  $N \rightarrow \infty$ .

There are two critical components in the non-rigorous argument that we presented in this section: (i) the Gaussian shape of the wave when  $N$  is very large, and (ii) the relation between the speed of the mean and that of the front of the wave. The second component above has a rigorous counterpart in Proposition 4.2, but we have found it difficult to give a rigorous statement of the shape of the wave that we can prove and use, therefore our rigorous arguments in §4 does not rely on the first component of the non-rigorous argument. What takes its place is a comparison argument between the selected process and the neutral process with only the mutation and resampling mechanisms.

#### 4. Stationary Measure of the Centred Process

If  $2q-1 > 0$ , then the distribution  $P$  tends to move to the right by mutation and the selection mechanism also works to increase the mean fitness, therefore no stationary measure for  $P$  can exist. If  $2q-1 < 0$ , the mutation mechanism works to decrease the mean fitness but it is not at all clear the selection mechanism can keep the effects of deleterious mutations in check and maintain a ‘mutation-selection balance’. However, the process centred about its mean does have a stationary measure and our first task in this section is to establish this. Define

$$\hat{P}_k = p_{k+m(p)}$$



for  $p \in S^{(N)}$  and  $k \in \mathbb{Z}/N$ , so that  $m(\hat{p}) = 0$  for all  $p$ . Define

$$\begin{aligned} \hat{S}^{(N)} &= \{\hat{p} : \text{there is some } p \in S^{(N)} \text{ such that} \\ &\quad \hat{p}_k = p_{k+m(p)} \text{ for all } k \in \mathbb{Z}/N\}. \end{aligned}$$

We observe that every  $\hat{p} \in \hat{S}^{(N)}$  has all its mass on points spaced 1 apart and furthermore, the centred process  $\hat{P}$  is irreducible, i.e. all states in  $\hat{S}^{(N)}$  communicate. To get from state any  $\hat{p}_1$  to any  $\hat{p}_2$ , it suffices to first get to a state where all individuals have the same fitness type. For example, the following event ensures that at time  $t+h$ , all individuals will have the same number of mutations as carried by individual 1 at time  $t$ :

$$\begin{aligned} \max_{i,j} \Lambda_{1i,b}^{(N)}(t, t+h] + \Lambda_{1i,d}^{(N)}(t, t+h] + \Lambda_{2ij}^{(N)}(t, t+h] &= 0 \\ \min_i \Lambda_{3i1}^{(N)}(t, t+h] \geq 1, \max_i \sum_{j>1} \Lambda_{3ij}^{(N)}(t, t+h] &= 0. \end{aligned} \quad (11)$$

Then one can get to any configuration in  $\hat{S}^{(N)}$  by the mutation mechanism alone. The fact that the event in (11) has positive probability also ensures that the centred process is positive recurrent. By standard results, e.g. Theorem 3.5.3 of Norris (1997), the centred process  $\hat{P}$  is ergodic.

**Proposition 4.1.** *The centred process  $(\hat{P}, X - m(P))$  is ergodic, i.e. there is a unique stationary measure  $\pi$  and regardless of initial condition, the chain converges to the stationary measure as  $t \rightarrow \infty$ .*

From now on, we take

$$\begin{aligned} \bar{S}^{(N)} &= \{\bar{p} : \text{there is some } p \in S^{(N)} \text{ and } l \in \mathbb{Z}/N \text{ such that} \\ &\quad \bar{p}_k = p_{k+l} \text{ for all } k \in \mathbb{Z}/N\} \end{aligned}$$

to be as our state space for the process  $P$  because we may wish to start the process with an initial configuration that has all its mass spaced 1 apart but not necessarily falling onto  $\mathbb{Z}$ . Let  $\mathbb{E}^\pi$  denote the expectation started from the stationary measure  $\pi$ . Let  $T(t)$  be the semigroup associated with the process  $(P, X)$ , then since

$$\int \mathbb{E}^P[c_2(P(u))] d\pi(p) = \int T(u)c_2(p) d\pi(p) = \int c_2(p) d\pi(p),$$

we have

$$\begin{aligned} \mathbb{E}^\pi[m(P(t))] &= \int_0^t \int \mathbb{E}^P[\mu(2q-1) + sc_2(P(u))] d\pi(p) du \\ &= \mu(2q-1)t + s \int_0^t \int \mathbb{E}^P[c_2(\hat{P}(u))] d\pi(p) du \\ &= (\mu(2q-1) + s\mathbb{E}^\pi[c_2])t. \end{aligned} \quad (12)$$



Thus it suffices to estimate  $\mathbb{E}^\pi[c_2]$  in order to get a handle on the asymptotic speed at which  $m(P)$  increases. Such an approach resembles the one taken by Desai and Fisher (2007). However, we have found it difficult to estimate  $\mathbb{E}^\pi[c_2]$ . Instead, we use the relation between the speed of the mean and that of the front of the wave. For that, we define

$$k_c(p) = \max\{k : Np_{[k,\infty)} > \log^2 N\}. \quad (13)$$

which we view as the location of the front of the wave. Since  $k_c(p) - m(p) = k_c(\hat{p})$ , we arrive at the following

**Proposition 4.2.** *For all  $t \geq 0$ , with the stationary measure  $\pi$  of the centred process as the initial condition for the non-centred process  $P$ , we have*

$$\mathbb{E}^\pi[k_c(P(t)) - k_c(P(0))] = \mathbb{E}^\pi[m(P(t))].$$

Roughly speaking, the above proposition states that the speed of front of the wave is exactly the same as that of its mean, which seems to be obvious if the wave is of fixed shape. In the present setting, however, the shape of the wave is stochastic and this equality holds under the stationary measure of the centred wave. The idea of relating behaviour of the mean and the front of the wave has been used in our non-rigorous argument in §3, as well as in Rouzine *et al.* (2003). The idea of our main theorem, Theorem 4.6 below, is to start the process  $P(t)$  from the stationary measure of the centred process and obtain an  $\mathcal{O}(\log^{1-\delta} N)$  lower bound for the mean fitness of the population by time 1, as long as the proportion of beneficial mutations  $q$  is strictly positive. In this case, for large enough population sizes, the mean fitness of the population will increase at a rate roughly proportional to  $\log N$ . All results in what follows are valid for sufficiently large  $N$ , which we may not explicitly state all the time.

We first state three results that are needed for the proof of Theorem 4.6 below. Lemma 4.3 gives estimates on how far  $k_c(P)$  can retreat on sets of very small probabilities, while Lemma 4.4 compares the selected process with a neutral process to establish that if the population starts at time 0 with at least  $M$  (whose value range is specified in Lemma 4.4) individuals with fitness types  $\geq K_0$ , then the population is expected to have at least  $\log^2 N$  individuals with fitness types

$$\geq K_0 + 1.8 \log^{1-\epsilon} M,$$

where we observe that  $C_\mu(\sqrt{c_2(p)N^3} + N^2)e^{-Me^{-2(1+\mu)}/4}$  in the statement of Lemma 4.4 is a very small correction factor. Hence  $k_c(P(1))$  is expected to be at least  $K_0 + \log^{1-\epsilon} M$ . Finally, Proposition 4.5 states that for any initial condition  $p \in \bar{S}^{(N)}$ , the front is expected to advance at least  $1.7 \log^{1-5\beta} N$  minus a small correction factor.

**Lemma 4.3.** *Let  $A^{(N)} \subset \bar{S}^{(N)}$ . Let  $B^{(N)} \in \mathcal{F}_1$  be an event that satisfies  $\mathbb{P}^p(B^{(N)}) \leq \epsilon(N)$  for all  $p \in A^{(N)}$  where  $\epsilon(N) \rightarrow 0$  as  $N \rightarrow \infty$ . If  $N$  is*



sufficiently large, then for any  $p \in A^{(N)}$ ,

$$\mathbb{E}^p \left[ \inf_{t \in [0,1]} \min_{i=1,\dots,N} (X_i(t) - X_i(0)) \mathbf{1}_{B^{(N)}} \right] \geq -C_\mu \left( \sqrt{c_2(p)N^3} + N^2 \right) \epsilon(N)^{1/2},$$

where  $C_\mu$  is a constant depending only on  $\mu$ . In particular, if  $N$  is sufficiently large, then for any  $p \in A^{(N)}$ ,

$$\mathbb{E}^p \left[ \inf_{t \in [0,1]} (k_c(P(t)) - k_c(p)) \mathbf{1}_{B^{(N)}} \right] \geq -C_\mu \left( \sqrt{c_2(p)N^3} + N^2 \right) \epsilon(N)^{1/2}.$$

The result still holds if we replace the process  $(P, X)$  by the neutral process  $(P^{(Y)}, Y)$  defined in (17).

**Lemma 4.4.** Let  $t_1 \in [1/2, 1]$ ,  $K_0 \in \mathbb{Z}/N$ , and  $\epsilon \in (0, 1)$  be fixed. Let  $M = M(N)$  be a constant that depends on  $N$  such that

$$\frac{M}{e^{\log^{1-0.9\epsilon} M} \log^2 N} \rightarrow \infty$$

as  $N \rightarrow \infty$ . If  $N$  is sufficiently large, then for any  $p \in \bar{S}^{(N)}$  with  $p_{[K_0, \infty)} \geq M/N$ , we have

$$\mathbb{E}^p \left[ \inf_{t \in [t_1, 1]} k_c(P(t)) \right] \geq K_0 - C_\mu \left( \sqrt{c_2(p)N^3} + N^2 \right) e^{-Me^{-2(1+\mu)}/4} + 1.8 \log^{1-\epsilon} M.$$

**Proposition 4.5.** Let  $\mu > 0$ ,  $q > 0$  and  $s > 0$  be fixed. If  $N$  is sufficiently large, then for any  $\beta > 0$  and  $p \in \hat{S}^{(N)}$

$$\begin{aligned} \mathbb{E}^p[k_c(P(1)) - k_c(p)] &\geq 1.7 \log^{1-5\beta} N \\ &\quad - C_\mu \left( \sqrt{c_2(p)N^3} + \mathbb{E}^p \left[ \sqrt{c_2(P(t_0))N^3} \right] + N^2 \right) e^{-\frac{1}{2} \log^2 N}. \end{aligned}$$

where  $t_0 = \frac{2}{s} \log^{-\beta} N$ .

**Theorem 4.6.** Let  $\mu > 0$ ,  $q > 0$  and  $s > 0$  be fixed. Then for any  $\beta > 0$ ,

$$\mathbb{E}^\pi[m(P(1))] \geq \log^{1-6\beta} N$$

if  $N$  is sufficiently large.

*Proof.* We combine Propositions 4.2 and 4.5 to obtain

$$\begin{aligned} \mathbb{E}^\pi[m(P(1))] &= \mathbb{E}^\pi[k_c(P(1)) - k_c(p)] \\ &\geq 1.7 \log^{1-5\beta} N - C_\mu \left( N^{3/2} \mathbb{E}^\pi \left[ \sqrt{c_2} + \sqrt{c_2(P(t_0))} \right] + N^2 \right) e^{-\frac{1}{2} \log^2 N} \\ &= 1.7 \log^{1-5\beta} N - C_\mu \left( 2N^{3/2} \mathbb{E}^\pi[\sqrt{c_2}] + N^2 \right) e^{-\frac{1}{2} \log^2 N}. \end{aligned}$$

But from (12), we have

$$\mathbb{E}^\pi[m(P(1))] = \mu(2q - 1) + s\mathbb{E}^\pi[c_2].$$



Hence

$$(s + 2C_\mu N^{3/2} e^{-\frac{1}{2} \log^2 N}) \mathbb{E}^\pi[c_2] \geq 1.7 \log^{1-5\beta} N - \mu(2q-1) - C_\mu N^2 e^{-\frac{1}{2} \log^2 N},$$

which implies that

$$\mathbb{E}^\pi[c_2] \geq \frac{1.6}{s} \log^{1-5\beta} N$$

for sufficiently large  $N$ . The desired result follows.  $\square$

The rest of this work is devoted to the proof of Proposition 4.5, which makes use of Lemmas 4.3 and 4.4. We define

$$\begin{aligned} L &= \log^{1-3\beta} N \\ k_d(p) &= \max\{k : Np_{[k, \infty)} > e^{\log^{1-\beta} N}\}. \end{aligned}$$

The number of individuals beyond  $k_d$ ,  $e^{\log^{1-\beta} N}$ , is much larger than the number beyond  $k_c$  (which is  $\log^2 N$ ) but nevertheless is only a tiny proportion of the entire population. The basic idea for the proof of Proposition 4.5 is to use Lemma 4.4, which states that if there are  $M$  individuals with fitness types larger than  $K_0$  at time 0, then  $k_c(P)$  is expected to be beyond  $K_0 + 1.8 \log^{1-\epsilon} M$  at time 1, where the value of  $\epsilon$  does not depend on  $M$  as long as  $M$  is sufficiently large. We can then divide into 2 cases: (i) if  $k_d(P) \geq k_c(p) - L$  before some small time  $t_0$  (event  $B_1 \cup B_2$  below), and (ii) if  $k_d(P) < k_c(p) - L$  throughout the time interval  $[0, t_0]$  (event  $B_3 \cup B_4$  below). Under case (i), a simple application of Lemma 4.4 implies that the  $e^{\log^{1-\beta} N}$  individuals with fitness types larger than  $k_c(p) - L$  are expected to push  $k_c(P)$  to beyond  $k_c(p) - L + 2L$  at time 1, hence advancing  $k_c(P)$  by at least  $L$ . Under case (ii), the  $\log^2 N$  individuals with fitness types larger than  $k_c(p)$  will pick off individuals with fitness types smaller than  $k_c(p) - L$  (of which there are at least  $N - e^{\log^{1-\beta} N}$ ) via the selection mechanism at a very fast rate so that with very high probability by time  $t_0$ ,  $P_{[k_c(p), \infty)}(t_0)$  will be at least  $e^{\log^{1-4\beta} N}$ . Lemma 4.4 implies that these  $e^{\log^{1-4\beta} N}$  individuals will then push  $k_c(P)$  forward by at least  $e^{\log^{1-6\beta} N}$  by time 1. In either case, the front of the wave moves forward at a high speed.

**Proof of Proposition 4.5:** We take  $t_0 = \frac{2}{s} \log^{-\beta} N$  and define

$$\begin{aligned} T_0 &= \inf\{t \geq 0 : k_d(P(t)) \geq k_c(p) - L\} \\ B_1 &= \{P_{[k_c(p)-L, \infty)}(t_0) > e^{\log^{1-2\beta} N}, T_0 \leq t_0\} \\ B_2 &= \{P_{[k_c(p)-L, \infty)}(t_0) \leq e^{\log^{1-2\beta} N}, T_0 \leq t_0\} \\ B_3 &= \{P_{[k_c(p), \infty)}(t_0) > e^{\log^{1-4\beta} N}, T_0 > t_0\} \\ B_4 &= \{P_{[k_c(p), \infty)}(t_0) \leq e^{\log^{1-4\beta} N}, T_0 > t_0\}. \end{aligned}$$

We will estimate  $\mathbb{E}^p[(k_c(P(1)) - k_c(p)) \mathbf{1}_B]$  for  $B = B_1 \cup B_3$  and  $B = B_2 \cup B_4$ . For  $p \in \hat{S}^{(N)}$  with  $k_d(p) \geq k_c(p) - L$ ,  $T_0 = 0$ . But for those  $p$  with  $k_d(p) < k_c(p) - L$ ,



we need to establish that the number of individuals lying in  $[k_c(p), \infty)$  grows quickly, i.e.  $B_4$  has small probability. For that, we construct a set valued process  $I$  to be dominated by the set of individuals lying in  $[k_c(p), \infty)$ , i.e. such that  $I(t) \subset \{i : X_i(t) \in [k_c(p), \infty)\}$  for all  $t \leq T_0$ . Without any loss of generality, we assume that at time 0 individuals  $\{1, \dots, \log^2 N\}$  lie in  $[k_c(p), \infty)$  and define  $I(0) = \{1, \dots, \log^2 N\}$ . The mechanisms that drive the population  $P$  have the following effect on  $I$ :

1. Mutation: if any individual  $i \in I$  is hit by a deleterious mutation event, we delete  $i$  from  $I$ .
2. Selection: at a selection event when individual  $i \in I$  replaces individual  $j$  lying in  $(-\infty, k_d(P)]$  at time  $t$ , we add  $j$  to  $I$ ; at a selection event when individual  $i \in I$  is replaced by individual  $j \notin I$  at time  $t$  (in which case  $X_j > X_i$ ), we replace  $i \in I$  with  $j$ .
3. Resampling: at a resampling event when individual  $i$  replaces individual  $j$  at time  $t$  (which happens at rate  $\frac{1}{N}$ ), if  $i \notin I$  and  $j \in I$  then we delete  $j$  from  $I$ ; if  $i \in I$  and  $j \notin I$  then we add  $j$  to  $I$ .

Then for  $i \in I(t)$ , we have  $X_i(t) \in [k_c(p), \infty)$ , and  $|I|$  has the following transitions:

1. Mutation:  $|I|$  decreases by 1 at rate  $\mu(1 - q)|I|$ .
2. Selection:  $|I|$  increases by 1 at rate  $\frac{s}{N} \sum_{i \in I, j: X_j \leq k_d(P)} (X_i - X_j)^+$ .
3. Resampling:  $|I|$  increases by 1 and decreases by 1 both at rate  $|I| \frac{N - |I|}{N}$ .

Prior to  $T_0$ , we have

$$\begin{aligned} \frac{s}{N} \sum_{i \in I, j: X_j \leq k_d(P)} (X_i - X_j)^+ &\geq \frac{s}{N} \sum_{i \in I, j: X_j \leq k_d(P)} L \geq \frac{s}{N} |I| (N - e^{\log^{1-\beta} N}) L \\ &\geq 0.9s |I| L \end{aligned}$$

for sufficiently large  $N$ .

Let  $Z$  be an integer valued jump process with initial condition  $Z(0) = \log^2 N$  and the following transitions:

1.  $Z$  increases by 1 at rate  $0.9sLZ$
2.  $Z$  decreases by 1 at rate  $(\mu + 1)Z$ ,

then  $Z$  is dominated by  $|I|$  before  $T_0$ . By Lemma 5.2b, if we take  $t_0 = \frac{2}{s} \log^{-\beta} N$ , which is  $\geq \frac{1}{0.9sL - \mu - 1} (\log \frac{0.9sL}{\mu + 1} + \log^{1-4\beta} N)$  for sufficiently large  $N$ , then

$$\begin{aligned} \mathbb{P}^P(Z(t_0) \leq e^{\log^{1-4\beta} N}) &\leq \frac{1}{(1 - e^{-\log^{1-4\beta} N}) e^{\log^{1-4\beta} N}} \left( \frac{4(\mu + 1)}{0.9sL} \right)^{\log^2 N} \\ &\leq C e^{(\log^2 N)(\log C - \log L)} \\ &\leq C e^{-\log^2 N}. \end{aligned}$$

Since  $|I|$  dominates  $Z$  (i.e.  $|I(t)| \geq Z(t)$ ) and  $I$  is dominated by the set of



individuals lying in  $[k_c(p), \infty)$  before  $T_0$ , we have

$$\mathbb{P}^p(B_4) \leq C e^{-\log^2 N} \quad (14)$$

for all  $p \in \hat{S}^{(N)}$ .

Now we turn to the event  $B_2$ . Without any loss of generality, we assume at time  $T_0$ , individuals in  $A_0 = \{1, 2, \dots, \lceil e^{\log^{1-\beta} N} \rceil\}$  have fitness  $\geq k_c(p) - L$ . During the time period  $[T_0, t_0]$ , the number of resampling events where individual  $i \in A_0$  gets replaced by another individual is  $\text{Poisson}(\frac{N-1}{N}(t_0 - T_0))$ , so  $Y_i$  remains untouched by a resampling event during  $[0, 1]$  with probability  $\geq e^{-1}$ . Furthermore, no deleterious mutation event falls on  $Y_i$  during  $[T_0, t_0]$  with probability  $e^{-(1-q)\mu(t_0 - T_0)} \geq e^{-\mu}$ . Let

$$A_1 = \{i \in A_0 : X_i \text{ remains untouched by a resampling event} \\ \text{or a deleterious mutation event during } [T_0, t_0]\},$$

then  $|A_1|$  dominates  $\text{Binomial}(\lceil e^{\log^{1-\beta} N} \rceil, e^{-(1+\mu)})$ . By Lemma 5.1a, if  $p_{[K_0, \infty)} \geq M/N$ , then

$$\mathbb{P}^p(B_2) \leq e^{-e^{\log^{1-\beta} N} e^{-2(1+\mu)}/2}. \quad (15)$$

Combining this and (14) implies

$$\mathbb{P}^p(B_2 \cup B_4) \leq C e^{-\log^2 N}. \quad (16)$$

Hence by Lemma 4.3, we have, for any  $p \in \hat{S}^{(N)}$ ,

$$\mathbb{E}^p[(k_c(P(1)) - k_c(p)) \mathbf{1}_{B_2 \cup B_4}] \geq -C_\mu \left( \sqrt{c_2(p)N^3} + N^2 \right) e^{-\frac{1}{2} \log^2 N}.$$

Finally we turn to events  $B_1$  and  $B_3$ . Both these two events, unlike  $B_2$  and  $B_4$ , will turn out to make large and positive contribution to the rate of adaptation, and even though we have no estimates on their probabilities, we expect neither to tend to 0 as  $N \rightarrow \infty$ . On  $B_1$ , there are more than  $N e^{\log^{1-2\beta} N}$  individuals in  $[k_c(p) - L, \infty)$  at time  $t_0$ . And on  $B_3$ , at time  $t_0$ , there are more than  $N e^{\log^{1-4\beta} N}$  individuals in  $[k_c(p), \infty)$ , therefore for any  $p \in \hat{S}^{(N)}$ ,

$$\begin{aligned} & \mathbb{E}^p[(k_c(P(1)) - k_c(p)) \mathbf{1}_{B_1 \cup B_3}] \\ &= \mathbb{E}^p[\{\mathbb{E}^p[k_c(P(1)) | \mathcal{F}_{t_0}] - k_c(p)\} \mathbf{1}_{B_1 \cup B_3}] \\ &= \mathbb{E}^p\left[\left\{\mathbb{E}^{P(t_0)}[k_c(P(1 - t_0))] - k_c(p)\right\} \mathbf{1}_{B_1 \cup B_3}\right] \\ &\geq \mathbb{E}^p\left[\left(-L - C_\mu \left(\sqrt{c_2(P(t_0))N^3} + N^2\right) e^{-N e^{-2(1+\mu)}/8} + 1.8 \log^{1-\beta} \frac{N}{2}\right) \mathbf{1}_{B_1}\right] \\ &\quad + \mathbb{E}^p\left[\left(-C_\mu \left(\sqrt{c_2(P(t_0))N^3} + N^2\right) e^{-e^{\log^{1-4\beta} N} e^{-2(1+\mu)}/4}\right. \right. \\ &\quad \left. \left. + 1.8 \log^{1-\beta}(e^{\log^{1-4\beta} N})\right) \mathbf{1}_{B_3}\right] \\ &\geq 1.8(\log^{1-5\beta} N) \mathbb{P}^p(B_1 \cup B_3) - C_\mu e^{-\log^2 N} \mathbb{E}^p\left[\sqrt{c_2(P(t_0))N^3} + N^2\right], \end{aligned}$$



where in the first  $\geq$ , we use Lemma 4.4 twice, with  $K_0 = k_c(p) - L$ ,  $M = N/2$ , and  $\epsilon = \beta$  for event  $B_1$ , and with  $K_0 = k_c(p)$ ,  $M = e^{\log^{1-4\beta} N}$ , and  $\epsilon = \beta$  for event  $B_3$ .

We combine the two estimates above to obtain that if  $N$  is sufficiently large, then for any  $p \in \hat{S}^{(N)}$ ,

$$\begin{aligned}
& \mathbb{E}^p[k_c(P(1)) - k_c(p)] \\
&= \mathbb{E}^p[(k_c(P(1)) - k_c(p))\mathbf{1}_{B_1 \cup B_3}] + \mathbb{E}^p[(k_c(P(1)) - k_c(p))\mathbf{1}_{B_2 \cup B_4}] \\
&\geq 1.8(\log^{1-5\beta} N)\mathbb{P}^p((B_2 \cup B_4)^c) - C_\mu e^{-\log^2 N} \mathbb{E}^p \left[ \sqrt{c_2(P(t_0))N^3} + N^2 \right] \\
&\quad - C_\mu \left( \sqrt{c_2(p)N^3} + N^2 \right) e^{-\frac{1}{2} \log^2 N} \\
&\geq 1.7(\log^{1-5\beta} N) - C_\mu \left( \sqrt{c_2(p)N^3} + \mathbb{E}^p \left[ \sqrt{c_2(P(t_0))N^3} \right] + N^2 \right) e^{-\frac{1}{2} \log^2 N},
\end{aligned}$$

where we use (16) in the last inequality. Hence we have the desired result.  $\square$

## 5. Proof of Supporting Lemmas

The lemmas in this section are needed for the proof of Proposition 4.5. Lemma 5.1 gives large deviation estimates for the binomial and Poisson random variables. Lemma 5.2 establishes a few results on a birth-death process, which we will use to show that fit individuals pick off unfit individuals very quickly via the selection mechanism. We then prove Lemmas 4.3 and 4.4.

**Lemma 5.1.** (a) Suppose  $Z \sim \text{Binomial}(n, \gamma)$ , then  $P(Z \leq n\gamma/2) \leq e^{-n\gamma^2/2}$ .  
(b) Suppose  $\lambda > 0$  is fixed and  $Z \sim \text{Poisson}(\lambda)$ , then  $P(Z \geq n) \geq \frac{e^{-\lambda - \frac{1}{2n}}}{\sqrt{2\pi}} \left(\frac{\lambda}{n^2}\right)^n$ .  
In particular, if  $\epsilon > 0$  is fixed and  $P(Z \geq 2\log^{1-\epsilon} M) \geq c_{(1)} \exp(-\log^{1-0.9\epsilon} M)$  for some constant  $c_{(1)}$  and sufficiently large  $M$ .  
(c) Suppose  $Z \sim \text{Poisson}(N\mu)$ , then  $P(Z \geq N^2) \leq Ce^{-N \log N}$ .

*Proof.* (a) We use Hoeffding's inequality (Hoeffding 1963) to prove this:

$$\begin{aligned}
& \text{Let } X_1, \dots, X_n \text{ be i.i.d. random variables taking values in } [a, b]. \text{ Let} \\
& U = X_1 + \dots + X_n \text{ and } t > 0, \text{ then } P(U - E[U] \geq nt) \leq e^{-2nt^2/(b-a)^2}.
\end{aligned}$$

We regard the binomial random variable  $n - Z$  as a sum of  $n$  independent *Bernoulli*( $1 - \gamma$ ) random variables, then

$$\begin{aligned}
P(Z \leq n\gamma/2) &= P(n - Z \geq n(1 - \gamma/2)) \\
&= P((n - Z) - n(1 - \gamma) \geq n(1 - \gamma/2) - n(1 - \gamma)) \\
&= P((n - Z) - n(1 - \gamma) \geq n\gamma/2) \\
&\leq e^{-n\gamma^2/2}
\end{aligned}$$

by Hoeffding's inequality.



(b) By Stirling's formula (see e.g. page 257 of Abramowitz & Stegun 1965),  $k! < \sqrt{2\pi} k^{k+\frac{1}{2}} e^{-k+\frac{1}{2k}}$  for any integer  $k$ . Therefore for  $n \geq 1$ ,

$$\begin{aligned} P(Z \geq n) &= \sum_{k=n}^{\infty} \frac{e^{-\lambda} \lambda^k}{k!} \geq e^{-\lambda} \sum_{k=n}^{\infty} \frac{\lambda^k}{\sqrt{2\pi} k^{k+\frac{1}{2}} e^{-k+\frac{1}{2k}}} \\ &\geq e^{-\lambda+n-\frac{1}{2n}} \frac{\lambda^n}{\sqrt{2\pi} n^{n+\frac{1}{2}}} \geq \frac{e^{-\lambda-\frac{1}{2n}}}{\sqrt{2\pi}} \frac{1}{\sqrt{n}} \left(\frac{\lambda}{n}\right)^n \geq \frac{e^{-\lambda-\frac{1}{2n}}}{\sqrt{2\pi}} \left(\frac{\lambda}{n^2}\right)^n. \end{aligned}$$

We take  $n = 2 \log^{1-\epsilon} M$ , then for sufficiently large  $M$ ,

$$\begin{aligned} \frac{e^{-\lambda-\frac{1}{2n}}}{\sqrt{2\pi}} \left(\frac{\lambda}{n^2}\right)^n &\geq \frac{c_{(1)}}{(4\lambda^{-1} \log^{2-2\epsilon} M)^{2 \log^{1-\epsilon} M}} \\ &= \frac{c_{(1)}}{\exp\{(2 \log^{1-\epsilon} M) \log(4\lambda^{-1} \log^{2-2\epsilon} M)\}} \\ &= c_{(1)} \exp\{-(\log^{1-0.9\epsilon} M)(2 \log^{-0.1\epsilon} M)(\log(4\lambda^{-1}) + (2-2\epsilon) \log \log M)\} \\ &\geq c_{(1)} \exp(-\log^{1-0.9\epsilon} M). \end{aligned}$$

(c) We take  $n = N^2$ , then

$$P(Z = n) = e^{-N\mu} \frac{(N\mu)^n}{n!} \leq e^{-N\mu} \frac{C}{\sqrt{n}} \left(\frac{N\mu e}{n}\right)^n \leq C \left(\frac{1}{N}\right)^N = Ce^{-N \log N},$$

where we apply Stirling's formula  $k! > \sqrt{2\pi} k^{k+\frac{1}{2}} e^{-k} > c\sqrt{k}(k/e)^k$ . Consequently,

$$\begin{aligned} P(Z \geq n) &= e^{-N\mu} \sum_{k=n}^{\infty} \frac{(N\mu)^k}{k!} \leq e^{-N\mu} \frac{(N\mu)^n}{n!} \sum_{k=0}^{\infty} \left(\frac{N\mu}{n}\right)^k \\ &= P(Z = n) \frac{n}{n - N\mu} \leq Ce^{-N \log N}, \end{aligned}$$

as required.  $\square$

**Lemma 5.2.** *Let  $Z$  be an integer valued jump process with initial condition  $Z(0) = Z_0 > 0$  and the following transitions:*

1.  $Z$  increases by 1 at rate  $aZ$
2.  $Z$  decreases by 1 at rate  $bZ$ ,

where  $a, b \geq 0$  and  $a \neq b$ , then

(a) For  $x \in [0, 1)$ ,

$$G(x, t) = E(x^{Z_t}) = \left( \frac{b(x-1) - (ax-b)e^{-(a-b)t}}{a(x-1) - (ax-b)e^{-(a-b)t}} \right)^{Z_0}.$$

(b) If  $a \geq b$ ,  $M \geq 1$  and  $t \geq (\log 2 \vee \log(aM/b))/(a-b)$ , then  $P(Z(t) \leq k) \leq \frac{1}{(1-1/M)^k} \left(\frac{4b}{a}\right)^{Z_0}$ .



*Proof.* (a) It can be shown that  $G(x, t)$  satisfies

$$\frac{\partial}{\partial t} G(x, t) = (ax - b)(x - 1) \frac{\partial}{\partial x} G(x, t)$$

and that the given  $G(x, t)$  satisfies this PDE with initial condition  $G(x, 0) = x^{Z_0}$ ; see for example Theorem 6.11.10 in Grimmett & Stirzaker (1992).

(b) We take  $x = 1 - 1/M$  and apply Markov's inequality to obtain

$$\begin{aligned} P(Z(t) \leq k) &= P(x^{Z(t)} \geq x^k) \leq \frac{E((1 - 1/M)^{Z(t)})}{(1 - 1/M)^k} \\ &= \frac{1}{(1 - 1/M)^k} \left( \frac{b + (a(M - 1) - bM)e^{-(a-b)t}}{a + (a(M - 1) - bM)e^{-(a-b)t}} \right)^{Z_0} \\ &\leq \frac{1}{(1 - 1/M)^k} \left( \frac{b + aMe^{-(a-b)t}}{a - ae^{-(a-b)t}} \right)^{Z_0}, \end{aligned}$$

where in the last inequality, we use the assumptions  $M \geq 1$  and  $a \geq b$  to deduce that  $(aM - bM)e^{-(a-b)t} \geq 0$ . Since  $t \geq (\log 2 \vee \log(aM/b))/(a - b)$ , we have  $aMe^{-(a-b)t} \leq b$  and  $ae^{-(a-b)t} \leq a/2$ . Therefore

$$P(Z(t) \leq k) \leq \frac{1}{(1 - 1/M)^k} \left( \frac{4b}{a} \right)^{Z_0},$$

as required.  $\square$

Before we prove Lemmas 4.3 and 4.4, we first construct a process  $Y$  consisting of individuals that undergo the mutation and resampling mechanisms of §2 but not the selection mechanism. Let  $Y_i(t) \in \mathbb{Z}/N$ ,  $i = 1, \dots, N$ , denote the number of mutations present in the  $i^{\text{th}}$  individual in the population, then

$$\begin{aligned} Y_i(t) &= Y_i(0) + \int_0^t \Lambda_{1i,b}^{(N)}(du) - \int_0^t \Lambda_{1i,d}^{(N)}(du) \\ &\quad + \sum_j \int_0^t (Y_j(u-) - Y_i(u-)) \Lambda_{3ij}^{(N)}(du). \end{aligned} \quad (17)$$

Let  $P^{(Y)}(t)$  be the empirical measure formed by the  $N$  individuals of the process  $Y$ . Since we use the same Poisson random measures and Poisson processes to construct  $X$  and  $Y$ , we have  $Y_i(t) \leq X_i(t)$  for all  $t \geq 0$  and  $i = 1, \dots, N$ , provided  $Y_i(0) \leq X_i(0)$  for all  $i$  at time 0.

**Proof of Lemma 4.3:** We prove the result for the neutral process  $(P^{(Y)}, Y)$ , then since  $X$  dominates  $Y$ , we have the desired result for  $(P, X)$  as well. Let

$$U = \inf_{t \in [0, 1]} \min_{i=1, \dots, N} (Y_i(t) - Y_i(0))$$

and  $p \in A^{(N)}$  be the initial configuration of the population. We only need a crude estimate on  $\mathbb{E}^p[U \mathbf{1}_{B^{(N)}}]$ . Let  $V_1$  be the total number of mutation events



(both deleterious and beneficial) and  $V_2$  be the total number of resampling events that fall on all individuals during  $[0, 1]$ , then  $V_1 \sim \text{Poisson}(N\mu)$  and  $V_2 \sim \text{Poisson}(2N)$ . Let

$$k_w(p) = \max\{k - l : p_k \neq 0, p_l \neq 0\}$$

be the width of the support of  $p$ . Since the resampling mechanism does not increase the width of the support,  $k_w(P(t)) \leq k_w(p) + V_1$  for all  $t \in [0, 1]$ . The most any individual's fitness can decrease due to a resampling event at  $t$  is  $k_w(P(t))$ , hence

$$-U \leq V_2(k_w(p) + V_1) + (V_2 + 1)V_1,$$

where the first term on the right accounts for the possible decrease in fitness due to each of the  $V_2$  resampling events and the second term accounts for the possible decrease due to mutation events between resampling events. Hence by Holder's inequality, for any  $p \in A^{(N)}$ ,

$$\begin{aligned} \mathbb{E}^p[|U| \mathbf{1}_{B^{(N)}}] &\leq k_w(p) (\mathbb{E}^p[V_2^2])^{1/2} (\mathbb{P}^p(B^{(N)}))^{1/2} \\ &\quad + (\mathbb{E}^p[(2V_2 + 1)^4])^{1/4} (\mathbb{E}^p[V_1^4])^{1/4} (\mathbb{P}^p(B^{(N)}))^{1/2} \\ &\leq C_\mu (k_w(p)N + N^2) \epsilon(N)^{1/2}. \end{aligned}$$

Since  $c_2(p) \geq \frac{1}{N}(k_w(p)/2)^2$  for any  $p \in \bar{S}^{(N)}$ , we have the desired result.  $\square$

**Proof of Lemma 4.4:** First we observe that the requirement

$$\frac{M}{e^{\log^{1-0.9\epsilon} M} \log^2 N} \rightarrow \infty \text{ as } N \rightarrow \infty \quad (18)$$

implies

$$\frac{M}{2} e^{-(1+\mu)} \geq \log^2 N \quad (19)$$

for sufficiently large  $N$ . Let  $Y$  be the neutral process defined in (17). If  $p \in \bar{S}^{(N)}$  and  $p_{[K_0, \infty)} \geq M/N$ , then at least  $M$  individuals lie in  $[K_0, \infty)$ . Without any loss of generality, we assume individuals  $1, \dots, M$  lie in  $[K_0, \infty)$ . We take the initial condition  $Y_i(0) = X_i(0)$  for all  $i = 1, \dots, N$ , then  $Y_i(t) \leq X_i(t)$  for all  $t \geq 0$  and  $i = 1, \dots, N$ . Let

$$A_2 = \{i \in \{1, \dots, M\} : Y_i \text{ remains untouched by a resampling event or a deleterious mutation event during } [0, 1]\},$$

then  $A_2$  is measurable with respect to the filtration generated by  $\Lambda_{1i,d}^{(N)}$  and  $\Lambda_{3ij}^{(N)}$  during the time period  $[0, 1]$  and independent from the filtration generated by  $\Lambda_{1i,b}^{(N)}$ . Furthermore, the same argument used for (15) implies that the



distribution of  $|A_2|$  dominates  $\text{Binomial}(M, e^{-(1+\mu)})$ . For  $p \in \bar{S}^{(N)}$ , we write

$$\begin{aligned} & \mathbb{E}^p \left[ \inf_{t \in [t_1, 1]} k_c(P^{(Y)}(t)) \right] \\ &= \mathbb{E}^p \left[ \inf_{t \in [t_1, 1]} k_c(P^{(Y)}(t)) \middle| |A_2| \geq \frac{M}{2} e^{-(1+\mu)} \right] \mathbb{P}^p \left( |A_2| \geq \frac{M}{2} e^{-(1+\mu)} \right) \\ & \quad + \mathbb{E}^p \left[ \inf_{t \in [t_1, 1]} k_c(P^{(Y)}(t)) \mathbf{1}_{\{|A_2| < M e^{-(1+\mu)}/2\}} \right] \end{aligned} \quad (20)$$

By Lemma 5.1a, if  $p_{[K_0, \infty)} \geq M/N$ , then

$$\mathbb{P}^p \left( |A_2| < \frac{M}{2} e^{-(1+\mu)} \right) \leq e^{-M e^{-2(1+\mu)}/2}. \quad (21)$$

We first deal with the conditional expectation involving the event  $\{|A_2| \geq \frac{M}{2} e^{-(1+\mu)}\}$  in (20). We observe that for the process  $Y$  and individuals in  $A_2$ , any change in their fitness is due to the beneficial mutation mechanism and therefore can only increase in time during  $[0, 1]$ . The number of beneficial mutations that fall on any individual during  $[0, t_1]$  is distributed  $\text{Poisson}(q\mu t_1)$  and since  $t_1 \geq 1/2$ , it dominates  $\text{Poisson}(q\mu/2)$ . Furthermore, it depends only on  $\Lambda_{1i,b}^{(N)}$ , therefore is independent of the set valued random variable  $A_2$ . Let  $K_1$  be the number of individuals in  $A_2$  that have their fitness types increase by at least  $2 \log^{1-\epsilon} M$  during  $[0, t_1]$ . If  $K_1 > \log^2 N$ , then  $\inf_{t \in [t_1, 1]} k_c(P^{(Y)}(t)) \geq K_0 + 2 \log^{1-\epsilon} M$ . Lemma 5.1b with  $\lambda = q\mu/2 > 0$  implies the following: conditioning on  $|A_2|$ , the distribution of  $K_1$  dominates  $\text{Binomial}(|A_2|, c_{(1)} \exp(-\log^{1-0.9\epsilon} M))$  for some constant  $c_{(1)}$ , and then Lemma 5.1a to obtain

$$\begin{aligned} & \mathbb{P}^p \left( \inf_{t \in [t_1, 1]} k_c(P^{(Y)}(t)) \geq K_0 + 2 \log^{1-\epsilon} M \middle| |A_2| \geq \frac{M}{2} e^{-(1+\mu)} \right) \\ & \geq \mathbb{P}^p \left( K_1 > \log^2 N \middle| |A_2| \geq \frac{M}{2} e^{-(1+\mu)} \right) \\ & \geq \mathbb{P}^p \left( K_1 > \frac{c_{(1)} M}{4} e^{-(1+\mu)} e^{-\log^{1-0.9\epsilon} M} \middle| |A_2| \geq \frac{M}{2} e^{-(1+\mu)} \right) \\ & \geq 1 - \exp \left( -\frac{c_{(1)}^2 M}{4} e^{-(1+\mu)} e^{-2 \log^{1-0.9\epsilon} M} \right) \\ & \geq 1 - \exp \left( -c_{(2)} e^{\log M - 2 \log^{1-0.9\epsilon} M} \right) \\ & \geq 1 - \exp \left( -c_{(2)} e^{0.9 \log M} \right), \end{aligned} \quad (22)$$

where  $c_{(2)}$  is a constant and we use (19) in the second inequality. By (18),  $\frac{M}{2} e^{-(1+\mu)} > \log^2 N$  for sufficiently large  $N$ , hence  $\inf_{t \in [t_1, 1]} k_c(P^{(Y)}(t)) \geq K_0$  on the event  $\{|A_2| \geq \frac{M}{2} e^{-(1+\mu)}\}$ . Therefore (22) implies

$$\mathbb{E}^p \left[ \inf_{t \in [t_1, 1]} k_c(P^{(Y)}(t)) \middle| |A_2| \geq \frac{M}{2} e^{-(1+\mu)} \right] \geq K_0 + 1.9 \log^{1-\epsilon} M.$$



Now we deal with the expectation in (20) involving the event  $\{|A_2| < \frac{M}{2}e^{-(1+\mu)}\}$ , which, by (21), has probability  $\leq e^{-Me^{-2(1+\mu)}/2}$  if  $p \in \bar{S}^{(N)}$  and  $p_{[K_0, \infty)} \geq M/N$ . We observe that for such  $p$ , there are more than  $\log^2 N$  individuals with fitness types  $\geq K_0$  at time 0, therefore  $k_c(p) \geq K_0$ . Hence Lemma 4.3 implies

$$\begin{aligned} \mathbb{E}^p \left[ \inf_{t \in [t_1, 1]} (k_c(P^{(Y)}(t)) - K_0) \mathbf{1}_{\{|A_2| < \frac{M}{2}e^{-(1+\mu)}\}} \right] \\ \geq -C_\mu \left( \sqrt{c_2(p)N^3} + N^2 \right) e^{-Me^{-2(1+\mu)}/4} \end{aligned}$$

if  $p_{[K_0, \infty)} \geq M/N$ . Plugging the above two estimates along with (21) into (20) yields for  $p$  with  $p_{[K_0, \infty)} \geq M/N$ ,

$$\begin{aligned} \mathbb{E}^p \left[ \inf_{t \in [t_1, 1]} k_c(P^{(Y)}(t)) \right] &\geq (K_0 + 1.9 \log^{1-\epsilon} M) \mathbb{P}^p \left( |A_2| \geq \frac{M}{2}e^{-(1+\mu)} \right) \\ &\quad + \mathbb{E}^p \left[ (k_c(P^{(Y)}(t_1)) - K_0) \mathbf{1}_{\{|A_2| < Me^{-(1+\mu)}/2\}} \right] + K_0 \mathbb{P}^p(|A_2| < \frac{M}{2}e^{-(1+\mu)}) \\ &\geq K_0 - C_\mu \left( \sqrt{c_2(p)N^3} + N^2 \right) e^{-Me^{-2(1+\mu)}/4} \\ &\quad + (1.9 \log^{1-\epsilon} M) \inf_{p \in \bar{S}^{(N)}: p_{[K_0, \infty)} \geq M/N} \mathbb{P}^p \left( |A_2| \geq \frac{M}{2}e^{-(1+\mu)} \right) \\ &\geq K_0 - C_\mu \left( \sqrt{c_2(p)N^3} + N^2 \right) e^{-Me^{-2(1+\mu)}/4} + 1.8 \log^{1-\epsilon} M. \end{aligned}$$

Since  $X$  dominates  $Y$ , we have the desired result.  $\square$

### Acknowledgements

The authors are grateful to Nick Barton for posing the initial problem, and to Nick Barton and Jonathan Coe for valuable discussions throughout this research. In addition, we thank three anonymous referees for valuable advice and suggestions, one of whom pointed out the existence of a stationary measure for the centred process, while another one pointed us to the reference on Lambert  $W$  functions.

### References

- [1] M. Abramowitz and I. A. Stegun. *Handbook of Mathematical Functions*. Dover, 1965.
- [2] N. H. Barton. Linkage and the limits to natural selection. *Genetics*, 140:821–841, 1995.
- [3] N. H. Barton and J. B. Coe. An upper limit to the rate of adaptation. *Preprint*, 2007.
- [4] E. Brunet, B. Derrida, A. H. Muller, and S. Munier. Noisy travelling waves: effect of selection on genealogies. *Europhys. Lett.*, 76:1–7, 2006.
- [5] R. M. Corless, G. H. Gonnet, D. E. G. Hare, D. J. Jeffrey, and D. E. Knuth. On the Lambert  $W$  function. *Advances in Computational Mathematics*, 5:329–359, 1996.



- [6] C. Cuthbertson, A. M. Etheridge, and Feng Yu. Fixation probability for competing selective sweeps. *Preprint, arXiv:0812.0104*, 2008.
- [7] M. M. Desai and D. S. Fisher. Beneficial mutation-selection balance and the effect of linkage on positive selection. *Genetics*, 176:1759–98, 2007.
- [8] A. M. Etheridge, P. Pfaffelhuber, and A. Wakolbinger. An approximate sampling formula under genetic hitchhiking. *Ann. Appl. Probab.*, 16(2):685–729, 2006.
- [9] A. M. Etheridge, P. Pfaffelhuber, and A. Wakolbinger. How often does the ratchet click? facts, heuristics, asymptotics. In *Trends in Stochastic Analysis*, 2007 (to appear).
- [10] J. Felsenstein. The evolutionary advantage of recombination. *Genetics*, 78(2):737–756, 1974.
- [11] R. A. Fisher. *The Genetical Theory of Natural Selection*. Clarendon Press, Oxford, 1930.
- [12] P. J. Gerrish and R. E. Lenski. The fate of competing beneficial mutations in an asexual population. *Genetica*, 102/103:127–144, 1998.
- [13] J. H. Gillespie. *The Causes of Molecular Evolution*. Oxford University Press, 1991.
- [14] I. Gordo and B. Charlesworth. On the speed of Muller’s ratchet. *Genetics*, 156:2137–2140, 2000.
- [15] G. R. Grimmett and D. R. Stirzaker. *Probability and Random Processes*. The Clarendon Press Oxford University Press, New York, second edition, 1992.
- [16] J. Haigh. The accumulation of deleterious genes in a population. *Theor. Popul. Biol.*, 14(2):251–267, 1978.
- [17] J. B. S. Haldane. A mathematical theory of natural and artificial selection, part v: Selection and mutation. *Proceedings of the Cambridge Philosophical Society*, 23:834–44, 1927.
- [18] M. Hegreness, N. Shores, D. Hartl, and R. Kishony. An equivalence principle for the incorporation of favourable mutations in asexual populations. *Science*, 311:1615–1617, 2006.
- [19] Paul Higgs and Glenn Woodcock. The accumulation of mutations in asexual populations, and the structure of genealogical trees in the presence of selection. *J. Math. Biol.*, 33:677–702, 1995.
- [20] W. G. Hill and A. Robertson. The effect of linkage on limits to artificial selection. *Genetics Research*, 8:269–294, 1966.
- [21] W. Hoeffding. Probability inequalities for sums of bounded random variables. *Journal of the American Statistical Association*, 58 (301):13–30, 1963.
- [22] N. Ikeda and S. Watanabe. *Stochastic Differential Equations and Diffusion Processes*. North-Holland mathematics library, 1981.
- [23] H. J. Muller. The relation of recombination and mutational advance. *Mutat. Res.*, 106:2–9, 1964.
- [24] J. R. Norris. *Markov Chains*. Cambridge University Press, 1997.
- [25] I. S. Novella, S. F. Elena, A. Moya, E. Domingo, and J. J. Holland. Size of genetic bottlenecks leading to virus fitness loss is determined by mean



- initial population fitness. *J. Virol.*, 69:2869–2872, 1995.
- [26] I. S. Novella, S. F. Elena, A. Moya, E. Domingo, and J. J. Holland. Exponential fitness gains of rna virus populations are limited by bottleneck effects. *J. Virol.*, 73:1668–1671, 1999.
  - [27] H Allen Orr. The rate of adaptation in asexuals. *Genetics*, 155:961–968, 2000.
  - [28] Philip Protter. *Stochastic Integration and Differential Equations*, volume 21 of *Applications of Mathematics (New York)*. Springer-Verlag, Berlin, 2003.
  - [29] I. Rouzine, E. Brunet, and C. O. Wilke. The traveling wave approach to asexual evolution: Muller’s ratchet and speed of adaptation. *Preprint, arXiv:0707.3469*, 2007.
  - [30] I. Rouzine, J. Wakeley, and J. M. Coffin. The solitary wave of asexual evolution. *Proceedings of the National Academy of Sciences*, 100(2):587–592, 2003.
  - [31] W. Stephan, L. Chao, and J. Smale. The advance of Muller’s ratchet in a haploid asexual population: approximate solution based on diffusion theory. *Genet. Res.*, 61:225–232, 1993.
  - [32] Michael E. Taylor. *Partial Differential Equations*, volume 23 of *Texts in Applied Mathematics*. Springer-Verlag, New York, 1996.
  - [33] Claus O. Wilke. The speed of adaptation in large asexual populations. *Genetics*, 167:2045–2054, 2004.
  - [34] Feng Yu and A. M. Etheridge. Rate of adaptation of large populations. In *Evolutionary Biology from Concept to Application*. Springer, 2008.